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10/680,963	10/07/2003	Piotr Bobrowicz	GFI-108	6071

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EXAMINER	
QIAN, CELINE X	
ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/680,963	BOBROWICZ ET AL.	
	Examiner	Art Unit	
	Celine X. Qian Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17, 22-24, 32, 35-37, 55-96* is/are pending in the application.

4a) Of the above claim(s) *1-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-17, 22-24, 32, 35-37, 55-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 December 2004* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0807*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-17, 22-24, 32, 35-37, 55-96 are pending in the application. Claims 1-12 are withdrawn from consideration for being directed to non-elected subject matter. Claims 13-17, 22-24, 32, 35-37, 55-96 are currently under examination.

This Office Action is in response to the Amendment filed on 8/27/07.

Response to Amendment

The objection to claims 22-24 and 36-39 has been withdrawn in light of the amendment.

The rejection of claims 13-17, 22-24, 32-39 under 35 U.S.C.112 2nd paragraph has been withdrawn in light of the amendment.

The rejection of claims 13-17, 22-24, 32, 35-37 under 35 U.S.C.112 1st paragraph is maintained for reason set forth of the record mailed on 4/20/07 and further discussed below.

The amendment to specification of paragraph [0001] is acknowledged and entered.

The amendment to specification of paragraph [090] is objected to for following reasons.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-17, 22-24, 32, 35-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In response to this rejection, Applicants argue that claims 13 and 14 have been amended to recite a "lower eukaryotic host cell engineered to produce a glycoproteins having hybrid or complex N-glycans." Applicants further explained the difference of the glycosylation differences and similarities between the glycosylation pathways in lower eukaryotes compared to the pathway in higher eukaryotes using Figure 1 as an example. Applicants further explain that "yeast and fungal cells do not contain a mannosidase capable of converting Man8GlcNAc2 or Man5-12GlcNAc2 N-glycans to a Man5GlcNAc2 N-glycan that can then be processed to hybrid or complex N-glycans. However, by introducing an alpha-1,2 mannosidase into yeast or fungal cells that do not have initiating alpha-l,6 mannosyltransferase activity, a lower eukaryotic host cell is created that produces glycoproteins that have predominantly Man5GlcNAc2 N-glycans. The Man5GlcNAc2 structure is the precursor N-glycan structure that in higher eukaryotes is then modified to make various complex N-glycans. The ability to modify lower eukaryotes to produce Man5GlcNAc2 structures is key because it is the precursor for all downstream processing steps. In the instant application, the applicants use yeast as a model to illustrate how to make lower eukaryotic host cells that produce glycoproteins having a hybrid N-glycan structure (GlcNAcMan5GlcNAc2) or a complex N-glycan structure (GlcNAc2Man3GlcNAc2, GlcNAcMan3GlcNAc2, GlcNAcMan4GlcNAc2)." Moreover, Applicants assert "Lower eukaryotic cells that are deficient in or lack alpha-1,6 mannosyltransferase activity can be obtained, produced, or acquired by any means. *Pichia pastoris, K. lactis, and Saccharomyces cerevisiae are* but three examples of unicellular fungal host cells which have been genetically

engineered to lack alpha-1,6 mannosyltransferase activity or in which mutants have been identified that lack alpha-1,6 mannosyltransferase activity. In yeast, the alpha-1,6 mannosyltransferase activity is encoded by the gene designated as *OCH1* and associated with hypermannosylation of glycoproteins in many lower eukaryotes and yeast that lack alpha-1,6 mannosyltransferase activity will produce glycoproteins wherein the predominant N-glycan has a Man8GlcNAc2 core structure (Compare Figure 5C with Figure 5B). The application teaches how to identify the *OCH1* gene in unicellular fungal cells (Examples 1 *(Pichia pastoris) and 9 (K. lactis)* and how to obtain host cells lacking alpha-1,6 mannosyltransferase activity (Examples 4 and 9). In contrast to yeast, *Aspergillus and Trichoderma are* multi-cellular or filamentous fungal species that naturally lack alpha-1,6 mannosyltransferase activity *(See* Maras *et al.* Glycoconjugate J. 16:99-107 (1999) (Attached as Exhibit A)." Once a lower eukaryotic host cell that is deficient in or lack alpha-1,6 mannosyltransferase activity has been obtained (e.g., yeast or other fungal cell), the host cells can be further modified to include an alpha-1,2 mannosidase activity and a GnT I activity to produce a hybrid GlcNAcMan5GlcNAc2 N-glycan structure, or further include a mannosidase II activity to produce a complex GlcNAcMan3GlcNAc2 or GlcNAcMan4GlcNAc2 N-glycan structure, or further a GnT II to produce a complex GlcNAc2Man3GlcNAc2 N-glycan structure." Applicants assert that the examples given in the specification teaches using yeast cell as a model that are deficient in alg3 and alpha-1, 6 mannosyltransferase activity, further include an alpha-1,2 mannosidase activity and a GnT I activity produces GlcNAcMan3GlcNAc2, wherein other types of complex and hybrid N-glycan may be produced when corresponding enzymes are introduced to said host cell. Applicants assert that since Alg3 is highly conserved across eukaryotes, there is a high probability of

success to produce lower eukaryotes that lack Alg3 activity. Applicants further argue that the skilled artisan would be able to use the method taught in the specification to genetically engineer the claimed host cells that is capable of making glycoproteins having a complex N-glycan structure. Applicants thus conclude that the written description requirement is met.

The above arguments have been fully considered but deemed unpersuasive. The reasons for lack of sufficient description for the claims are given in the office action mailed on 4/20/07. In response to the above arguments, the examiner acknowledges that the examples given in the specification provides a novel method for engineering yeast host cells that are capable of producing complex and hybrid glycoproteins. However, as indicated in the previous office action, the claimed genus encompasses a large number of lower eukaryotes, including animal, plant, algae, insect cells that comprises different glycosylation pathway than that of a yeast. Figure 1 illustrates the glycosylation pathway of yeast and human cells. The example given in the specification is limited to the engineering of a yeast host cell to produce complex or hybrid glycoproteins. However, since other types of lower eukaryotes possess different glycosylation pathway, whether applying the same approach to other types of eukaryotes such as animal, plant and insect would produce the same result is unpredictable. Indeed, as indicated by Maras et al.(exhibit A submitted by Applicants), hyperglycosylation is not a typical feature for filamentous fungi (see page 101, 1st col., 2nd paragraph). As such, whether engineering an Alg3 deficient strain of filamentous fungi and introducing mannosidase and GnTI to such host cell would result in the production of GlcNAcMan3GlcNAc2 is not predictable. To satisfy the statue of 112 1st paragraph, the specification must describe the claimed genus by a representative number of species by their complete structure or other relevant identifying characteristics. Since

the specification only gives the example for yeast host cells, it does not describe a representative number of species by their complete structure in view of the broad genus which include animal, plant, algae, insect and multicellular host cells. The relationship between the enzymes and substrates of the glycosylation pathway in yeast does not represent the same relationship in other types of lower eukaryotic host cells. As such, the relationship between the structure of the claimed genus of host cells and their function of producing complex and hybrid glycan is missing because the relationship described in yeast cannot be extrapolate to the broad genus of all lower eukaryotic cells. What's known in the art is not sufficient to make up such deficiency. A skilled artisan cannot predict the structure of the claimed host cell based on the function because one cannot envision what's not described. Furthermore, testing or assays to identify the claimed host cell themselves do not constitute sufficient description because they do not describe the structure of the claimed genus of lower eukaryotic cells. Therefore, the instant specification does not provide adequate description for the claimed invention.

Newly added claims 55-75 are rejected for same reason as set forth in the previous office action and reasons discussed above. Claims 76-96, drawn to a yeast host cell are rejected for reason set forth below. As indicated in the instant specification and the response filed on 8/27/07, it is apparent that once a lower eukaryotic host cell that is deficient in or lack alpha-1,6 mannosyltransferase activity has been obtained, the host cells can be further modified to include an alpha-1,2 mannosidase activity and a GnT I activity to produce a hybrid GlcNAcMan5GlcNAc2 N-glycan structure. As such, for a yeast host cell comprising GnTIII activity only, it cannot produce a complex or hybrid N-glycan. Since the specification does not describe other types of engineering process without at least the introduction of an alpha-1,2

mannosidase activity and a GnT I activity to produce the claimed yeast host cell, a representative number of species of the claimed yeast host cell have not been described. Therefore, this rejection also applies to these claims.

Specification

The amendment filed on 8/27/07 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the deletion of the text in [0090] changes the scope of the definition of a lower eukaryotic cell.

Applicant is required to cancel the new matter in the reply to this Office Action.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joe Woitach Ph.D. can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Celine X Qian Ph.D.
Examiner
Art Unit 1636

CELINE QIAN, PH.D.
PRIMARY EXAMINER